IB/2004/02654

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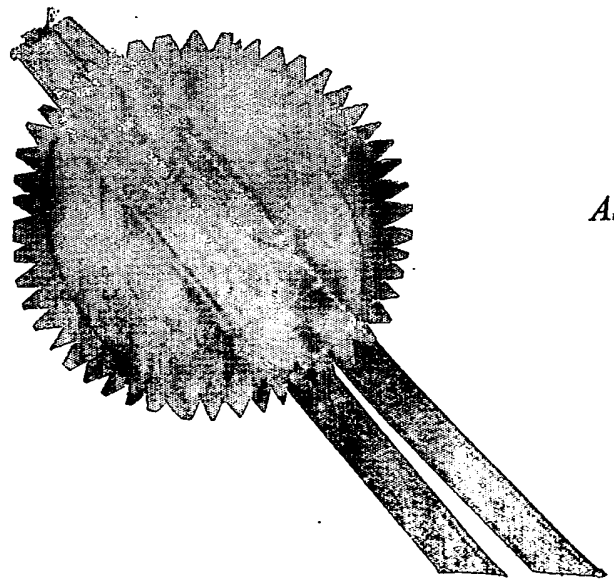
INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
W - 5, WEST PATEL NAGAR
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Provisional Specification*** *filed in connection with Application for Patent No.****1003/Del/2003*** *dated* ***14th August 2003.***

Witness my hand this 3rd day of November 2004.



(S.K. PANGASA)
Assistant Controller of Patents & Designs

FORM 1 1003 DEL 03

THE PATENTS ACT, 1970

14 AUG 2003

(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5(2), 7, 54 and 135; and rule 39)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"PHARMACEUTICAL COMPOSITIONS OF NATEGLINIDE TABLET"**

(b) that the Provisional Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. ROMI BARAT SINGH
b. PANANCHUKUNNATH MANOJ KUMAR
c. VISHNUBHOTLA NAGA PRASAD
d. SANJEEV KUMAR SETHI

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows: **NOT APPLICABLE**

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: **NOT APPLICABLE**

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on ..... Under section 16 of the Act. **NOT APPLICABLE**

7. That we are the assignee or legal representatives of the true and first inventors.

8. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana). INDIA.

9. Following declaration was given by the inventors or applicants in the convention country:
We, ROMI BARAT SINGH, PANANCHUKUNNATH MANOJ KUMAR, VISHNUBHOTLA NAGA PRASAD, SANJEEV KUMAR SETHI of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention or applicant in the convention country declare that the applicant herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. Romi Singh
(ROMI BARAT SINGH)

b.
(PANANCHUKUNNATH MANOJ KUMAR)

c.
(VISHNUBHOTLA NAGA PRASAD)

d.
(SANJEEV KUMAR SETHI)

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Followings are the attachment with the application:
a. Provisional Specification (3 copies)
b. Drawings (3 copies)
c. Priority document(s)
d. Statement and Undertaking on FORM – 3
e. Power of Authority (Not required)
f. Fee Rs.**3,000/-** (Rupees Three Thousand only..) in cheque bearing No.
dated : drawn on **HDFC Bank Limited, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **14TH** day of **August, 2003.**

For Ranbaxy Laboratories Limited

SKPatawari

(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM 2 1007-DEL-03

14 APR 2003

The Patents Act, 1970

(39 of 1970)

PROVISIONAL SPECIFICATION

(See Section 10)

PHARMACEUTICAL COMPOSITIONS OF NATEGLINIDE TABLET

RANBAXY LABORATORIES LIMITED

19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to pharmaceutical compositions of Nateglinide tablet.

Nateglinide is an amino acid derivative that lowers blood glucose levels by stimulating insulin secretion from the pancreas. It is widely indicated as monotherapy to lower blood glucose in patients with Type 2 diabetes. It is also indicated for use in combination with Metformin.

Presently Nateglinide oral tablets are available in 60mg or 120mg strengths and are marketed by Novartis under the trade name STARLIX.

US 6,559,188 describe compositions of Nateglinide or a pharmaceutically acceptable salt thereof. All the examples given in US 6559188 make use of lactose and microcrystalline cellulose as filler. The concentration of lactose being 34 to 36% w/w and microcrystalline cellulose 17 to 23% w/w, the total concentration of filler ranging from 50-70% w/w.

In the present invention we have found that nateglinide tablets can be prepared with sole filler. Further it can also be prepared with combination of lactose and microcrystalline cellulose as fillers wherein the concentration of lactose may be either less than 30% w/w or more than 50% w/w and similarly the concentration of microcrystalline cellulose may be less than 15% w/w or more than 25% w/w of the tablet.

Present invention provides more flexibility and choice of fillers. These fillers can be selected from the group comprising of corn starch, lactose, white sugar, sucrose, sugar compressible, sugar confectioners, glucose, sorbitol, calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose, fructose, kaolin, lactitol, mannitol, sorbitol, starch, starch pregelatinized, sucrose, and the like. In particular lactose, microcrystalline cellulose, mannitol or dicalcium phosphate can be used.

Hence in one aspect it provides a tablet composition comprising nateglinide or a pharmaceutically acceptable salt thereof and one filler.

In another aspect it provides a tablet composition comprising nateglinide or a pharmaceutically acceptable salt thereof and combination of two or more fillers.

In another aspect it provides a tablet composition comprising nateglinide or a pharmaceutically acceptable salt thereof and combination of lactose and microcrystalline cellulose as fillers, wherein the lactose is present in concentration of less than 30% w/w or more than 50% w/w and microcrystalline cellulose is present in a concentration of less than 15% w/w or more than 25% w/w of the total weight of tablet.

In another aspect it provides a tablet composition comprising nateglinide or a pharmaceutically acceptable salt thereof, at least one other antidiabetic compound and one filler.

In another aspect it provides a tablet composition comprising nateglinide or a pharmaceutically acceptable salt thereof; at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and metformin in each case in free form or in form of a pharmaceutically acceptable salt thereof; and one filler.

In another aspect it provides a tablet composition comprising nateglinide or a pharmaceutically acceptable salt thereof, at least one other antidiabetic compound and combination of two or more fillers.

In another aspect it provides a tablet composition comprising nateglinide or a pharmaceutically acceptable salt thereof; at least one other antidiabetic compound selected from the group consisting of glitazones, sulfonyl urea derivatives and metformin in each case in free form or in form of a pharmaceutically acceptable salt thereof; and combination of two or more fillers.

In another aspect it provides a tablet composition comprising nateglinide or a pharmaceutically acceptable salt thereof; at least one other antidiabetic compound; and combination of lactose and microcrystalline cellulose as fillers, wherein the lactose is present in concentration of less than 30% w/w or more than 50% w/w and microcrystalline cellulose is present in a concentration of less than 15% w/w or more than 25% w/w of the total weight of tablet.

In another aspect it provides a tablet composition comprising nateglinide or a pharmaceutically acceptable salt thereof and one filler for the preparation of a medicament for the prevention, delay of progression or treatment of metabolic disorders, in particular of type 2 diabetes mellitus or a disease or condition associated with diabetes mellitus.

In another aspect it provides a tablet composition comprising nateglinide or a pharmaceutically acceptable salt thereof and combination of two or more fillers for the preparation of a medicament for the prevention, delay of progression or treatment of metabolic disorders, in particular of type 2 diabetes mellitus or a disease or condition associated with diabetes mellitus.

In another aspect it provides a tablet composition comprising nateglinide or a pharmaceutically acceptable salt thereof and combination of lactose and microcrystalline cellulose as fillers, wherein the lactose is present in concentration of less than 30% w/w or more than 50% w/w and microcrystalline cellulose is present in a concentration of less than 15% w/w or more than 25% w/w of the total weight of tablet for the preparation of a medicament for the prevention, delay of progression or treatment of metabolic disorders, in particular of type 2 diabetes mellitus or a disease or condition associated with diabetes mellitus.

In another aspect it provides process for the preparation of nateglinide tablet compositions by wet granulation.

In another aspect it provides process for the preparation of nateglinide tablet compositions by dry granulation.

In another aspect it provides process for the preparation of nateglinide tablet compositions by direct compression.

The tablet pharmaceutical compositions as described herein may include other pharmaceutically acceptable excipients in addition to nateglinde and filler.

The term 'Nateglinide' as used herein includes Nateglinide base as well as pharmaceutically acceptable salts thereof.

The fillers can be selected from the group comprising of corn starch, lactose, white sugar, sucrose, sugar compressible, sugar confectioners, glucose, sorbitol, calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose, fructose, kaolin, lactitol, mannitol, sorbitol, starch, starch pregelatinized, sucrose, and the like. In particular lactose, microcrystalline cellulose, mannitol or dicalcium phosphate can be used. The concentration of filler can vary from 35-70% w/w of the tablet weight. When combination of lactose and microcrystalline cellulose is used lactose may be present in concentration of less than 30% w/w or more

than 50% w/w and microcrystalline cellulose may be present in a concentration of less than 15% w/w or more than 25% w/w of the total weight of tablet.

The term 'other pharmaceutically acceptable excipient' refers to ingredients of the composition, excluding the active drug substance.

Examples of other pharmaceutically acceptable excipients as used herein include binders, disintegrants, lubricants, glidants, colors and the like.

Examples of binders include methyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, gelatin, gum Arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and the like.

Examples of disintegrants include starch, croscarmellose sodium, crospovidone, sodium starch glycolate and the like.

Examples of lubricants and glidants include colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acids, microcrystalline wax, yellow beeswax, white beeswax and the like.

The coloring agents of the present invention may be selected from any FDA approved colors for oral use.

In one of the embodiments nateglinide tablet may be prepared by blending nateglinide, filler and disintegrant; granulating the blend with a binder solution; drying the granules; sizing; lubricating and compressing the lubricated granules.

In another embodiment nateglinide tablet may be prepared by blending nateglinide, filler, disintegrant and binder; granulating the blend with a solvent; drying the granules; sizing; lubricating and compressing the lubricated granules.

In another embodiment nateglinide tablet may be prepared by blending nateglinide, filler, disintegrant and binder; compacting or slugging the blend; breaking the slugs to make granules; lubricating and compressing the lubricated granules.

Granulation may be carried out in fluidized bed dryer and sizing can be done by milling or pulverization.

In another embodiment nateglinide tablet may be prepared by blending nateglinide, filler, disintegrant, binder and lubricant; and compressing.

The tablets prepared by the present invention may be coated with one or more additional layers comprising film forming agents and/or pharmaceutically acceptable excipients.

The coating layers over the tablet may be applied as solution/ dispersion of coating ingredients using any conventional technique known in the prior art such as spray coating in a conventional coating pan or fluidized bed processor; dip coating and the like.

Example of solvents used for preparing a solution/dispersion of the coating ingredients include methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water and the like and mixtures thereof.

Example of film forming agents include ethyl cellulose, Hydroxypropyl methylcellulose, Hydroxypropyl cellulose, methyl cellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl methyl phthalate, cellulose acetate, cellulose acetate trimelliatate, cellulose acetate phthalate; Waxes such as polyethylene glycol; methacrylic acid polymers such as Eudragit ® RL and RS; and the like and mixture thereof. Alternatively, commercially available coating compositions comprising film-forming polymers marketed under various trade names, such as Opadry® may also be used for coating.

The following examples are illustrative of the invention, and are not to be construed as limiting the invention.

EXAMPLE 1

Ingredient	**Example 1 (wt/tablet) mg**
Nateglinide	120
Lactose	425
Povidone	12
Croscarmellose sodium	20
Colloidal silicon dioxide	16
Purified water	q.s
Croscarmellose Sodium	12.8
Colloidal silicon dioxide	12.8
Magnesium stearate	11.4

PROCEDURE:

1. Nateglinide along with lactose, povidone, colloidal silicon dioxide and a part of croscarmellose sodium are mixed in a high shear mixer and granulated using purified water.
2. The wet granules are dried in a fluid bed drier, passed through a screen and then subjected to a pulverization step.
3. The colloidal silicon dioxide and the rest of the croscarmellose sodium are mixed, passed through a screen and blended with the granules of step 2.
4. The magnesium stearate is passed through a screen, blended with the blend of step 3 and the total mixture is compressed to tablets.

EXAMPLE 2-3

Ingredient	**Example 2 (wt/tablet) mg**	**Example 3 (wt/tablet) mg**
Nateglinide	120	120
Microcrystalline cellulose	253	425
Povidone	120	12
Croscarmellose sodium	40	20
Colloidal silicon dioxide	25	16
Purified water	q.s	q.s
Croscarmellose Sodium	20	12.8
Colloidal silicon dioxide	10	12.8
Magnesium stearate	12	11.4

PROCEDURE:

1. Nateglinide along with microcrystalline cellulose, povidone, colloidal silicon dioxide and a part of croscarmellose sodium are mixed in a high shear mixer and granulated using purified water.
2. The wet granules are dried in a fluid bed drier, passed through a screen and then subjected to a pulverization step.
3. The colloidal silicon dioxide and the rest of the croscarmellose sodium are mixed, passed through a screen and blended with the granules of step 2.
4. The magnesium stearate is passed through a screen, blended with the blend of step 3 and the total mixture is compressed to tablets.

EXAMPLE 4

Ingredient	Example 4 (wt/tablet) mg
Nateglinide	120
Mannitol	425
Povidone	12
Croscarmellose sodium	20
Colloidal silicon dioxide	16
Purified water	q.s
Croscarmellose Sodium	12.8
Colloidal silicon dioxide	12.8
Magnesium stearate	11.4

PROCEDURE:

1. Nateglinide along with mannitol, povidone, colloidal silicon dioxide and a part of croscarmellose sodium are mixed in a high shear mixer and granulated using purified water.
2. The wet granules are dried in a fluid bed drier, passed through a screen and then subjected to a pulverization step.
3. The colloidal silicon dioxide and the rest of the croscarmellose sodium are mixed, passed through a screen and blended with the granules of step 2.
4. The magnesium stearate is passed through a screen, blended with the blend of step 3 and the total mixture is compressed to tablets.

EXAMPLE 5

Ingredient	Example 5 (wt/tablet) mg
Nateglinide	120
Dicalcium Phosphate	425
Povidone	12
Croscarmellose sodium	20
Colloidal silicon dioxide	16

Purified water	q.s
Croscarmellose Sodium	12.8
Colloidal silicon dioxide	12.8
Magnesium stearate	11.4

PROCEDURE:

1. Nateglinide along with Dicalcium Phosphate, povidone, colloidal silicon dioxide and a part of croscarmellose sodium are mixed in a high shear mixer and granulated using purified water.
2. The wet granules are dried in a fluid bed drier, passed through a screen and then subjected to a pulverization step.
3. The colloidal silicon dioxide and the rest of the croscarmellose sodium are mixed, passed through a screen and blended with the granules of step 2.
4. The magnesium stearate is passed through a screen, blended with the blend of step 3 and the total mixture is compressed to tablets.

EXAMPLE 6-7

Ingredient	**Example 6 (wt/tablet) mg**	**Example 7 (wt/tablet) mg**
Nateglinide	120	120
Lactose	183	325
Microcrystalline cellulose	242	88
Povidone	12	12
Croscarmellose sodium	20	20
Colloidal silicon dioxide	16	28
Purified water	q.s	q.s
Croscarmellose Sodium	12.8	12.8
Colloidal silicon dioxide	12.8	12.8
Magnesium stearate	11.4	11.4

PROCEDURE:

1. Nateglinide along with lactose, povidone, colloidal silicon dioxide, microcrystalline cellulose and a part of croscarmellose sodium are mixed in a high shear mixer and granulated using purified water.

2. The wet granules are dried in a fluid bed drier, passed through a screen and then subjected to a pulverization step.
3. The colloidal silicon dioxide and the rest of the croscarmellose sodium are mixed, passed through a screen and blended with the granules of step 2.
4. The magnesium stearate is passed through a screen, blended with the blend of step 3 and the total mixture is compressed to tablets.

Further, it is contemplated that any single feature or any combination of optional features of the inventive variations described herein may be specifically excluded from the claimed invention and be so described as a negative limitation. Accordingly, it is not intended that the invention be limited, except as by the appended claims.

Dated 15TH day of **August, 2003.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary